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California EPA Office of Environmental Health Hazard Assessment Children's Environmental Health Initiative

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Children's Environmental Health Initiative
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ABSTRACT

The California legislature enacted a law requiring Cal/EPA's Office of Environmental Health Hazard Assessment (OEHHA) to evaluate whether our risk assessment methodologies are adequately protective of infants and children. In addition both OEHHA and the California Air Resources Board must examine whether the Ambient Air Quality Standards set for criteria air pollutants and health values for air toxics are adequately protective of infants and children. We have initiated a program to look at potential differences in response to toxicants between children and adults. We are evaluating this problem from the perspective of exposure differences as well as toxicokinetic and toxicodynamic differences between children and adults. Data on specific chemicals are rather limited. As a result, we will be pooling information to determine whether there are generic differences between children and adults that may be applicable to risk assessment in general. This paper discusses the rationale for approaching the problem of determining whether our risk assessment methods are adequate for infants and children and includes a discussion of the available information on both qualitative and quantitative differences in response to toxicants between children and adults or immature and mature laboratory animals. We will review examples of differences between children and adults in absorption, metabolism, and excretion of toxicants as well as qualitative differences in toxic response.

California EPA Office of Environmental Health Hazard Assessment's Children's Environmental Health Initiative

Interest in the evaluation of risks to children from environmental contaminants has intensified in recent years. In California it has culminated in the passage of legislation requiring the California Environmental Protection Agency to specifically consider children in setting Ambient Air Quality Standards (AAQS) and developing criteria for Toxic Air Contaminants (TACs). The Office of Environmental Health Hazard Assessment (OEHHA) is responsible for evaluating health effects information on the criteria air pollutants, ozone, carbon monoxide, sulfur oxides, nitrogen oxides, particulate matter, hydrogen sulfide, sulfates, and lead. It also provides health-based recommendations to the Air Resources Board (ARB) of AAQS for these compounds. In addition, OEHHA is responsible for conducting health effects assessments of TACs which are provided to the ARB for use in risk management activities. TACs include volatile carcinogens such as benzene and butadiene, heavy metals (lead, arsenic, mercury, manganese), lung irritants and toxicants (acrolein, formaldehyde), polychlorinated dibenzo-p-dioxins and congeners and related compounds (dibenzofurans, polychlorinated biphenyls). The legislation (SB 25, Escutia; chaptered 1999) requires OEHHA to consider in its health effects assessments and recommendations: (1) exposure patterns among infants and children that result in disproportionately high exposure: (2) special susceptibility of infants and children: (3) effects of simultaneous exposures to compounds with the same mechanism of action; and (4) any interactions of air pollutants. The law requires OEHHA, working with the ARB, to prioritize the AAQS for review based on whether they protect public health including that of infants and children. The law requires OEHHA to evaluate available information on the TACs and develop a list of TACs that potentially have disproportionate impacts on infants and children. In addition, OEHHA is required to re-evaluate existing health criteria (e.g. cancer potency factors, acute and chronic Reference Exposure Levels).

As a foundation for re-evaluating the health criteria for the TACs and criteria air pollutants, OEHHA is embarking on a major effort to evaluate our current risk assessment practices and their ability to protect infants and children. Our initial efforts have focused on gaining a better understanding of the physiological differences between infants, children and adults that impact both exposure and susceptibility. Underlying issues in response to chemical toxicants including pharmacokinetics and pharmacodynamics are particular areas of exploration. We have begun to evaluate pharmacokinetic modeling using child-specific parameters with a small subset of TACs. While there is a significant amount of information that can be gleaned from the literature that is applicable to evaluation of pharmacokinetic differences, there is little in the published literature that explores pharmacodynamic differences. Qualitative differences in response between young and mature animals are not uncommon. Interindividual variability in response due to genetic polymorphisms creates an additional complication in our risk assessment methods evaluation.

There is a paucity of data in the published literature that explores the toxic effects on children of environmental chemicals. It has been standard practice to base risk assessments on adults, using adult parameters and data obtained from occupational studies, or studies in mature laboratory animals. An exception to this is in risk assessments where the sensitive toxicological endpoint is developmental. There are a number of reasons to suspect that risk assessments based on adults may not adequately protect infants and children. The potential impact of environmental chemicals on child health may be affected by behavioral, physiologic, and sociological

differences factors that differ from those of adults. Children have limited diets and higher intakes per body weight of food, fluids and air. These may profoundly change exposure patterns, and along with many other differences, may result in significant illness or disabilities in children but not in a similarly exposed adult. Minamata disease, methylmercury poisoning, is one example in which prenatally exposed children were profoundly neurologically damaged by an exposure that was insufficient to produce clinical symptoms in the mother (Rogan 1995).

Risk assessment that specifically protects children presents challenges due to the many factors that must be considered, including rapid growth, changes in fluid and protein content, organ function, metabolic rates and enzymatic function that characterize childhood. A child's behavior as well as his/her environment allow for exposures that are both quantitatively and qualitatively different than adults. Premature infants, term newborns, children, and adolescents are age groups unique in all these parameters.

Limited scientific information is available even in immature test animals for unique age specific sensitivities. A developmental neurotoxicity testing protocol, published by the U.S. Environmental Protection Agency in 1991 and later revised (USEPA 1998), has not yet been used extensively to evaluate pesticides for registration or reregistration. An analysis by the Office of Pesticide Programs revealed that only 9 developmental neurotoxicity studies on pesticides had been submitted to the agency between 1991 and 1998 (Makris et al. 1998). Of these, six identified endpoints that suggested a qualitative difference in response between young animals and adults, leading to a more conservative risk assessment. These findings could not have been predicted by testing in mature animals only (Makris 2000).

In this article we will give examples of childhood differences that impact risk assessment practice and conclude with a summary of OEHHA's activities to include this developing body of knowledge into our risk assessment practice.

The Exposure Environment

Children's exposures are influenced by their activities and where they spend time. Compared to adults, they spend more time outdoors and in active play and sports. A study of activity patterns in California found that children under 12 years of age spent an average of 124 minutes per day engaged in active sports, hiking, or outdoor activities compared with only 21 minutes for adults (Wiley et al. 1991).

Newborns and young infants spend considerable time in a single environment (e.g. the crib) as opposed to moving about as older children do. An infant or toddler may be unable to remove herself from a noxious stimulant which may lead to increased exposure. Infants and young children frequently play on the floor and carpeting where they may contact cleaning agents, dust, formaldehyde, and possibly pesticide residues. These compounds may be absorbed through the skin or ingested during mouthing of hands, toys or other objects. As well, any vapors that are heavier than air will be concentrated in the breathing zone of young children near the floor. While the breathing zone for an adult is four to six feet above the floor for an infant it may be inches (Bearer 1995). In a tragic case in Michigan, a four-year-old child became acutely intoxicated from mercury used in indoor paint. Exposure was potentially greater for the child

because mercury vapor collects at floor level, and the breathing rate per unit of body weight is much higher in preschoolers than in adults. This resulted in acute poisoning of the child when no adults in the household were clinically affected (CDC 1990).

Chlorpyrifos, an organophosphate pesticide used in homes, has been shown to accumulate on sorbant surfaces such as children's plush toys and pillows for two weeks after application. Toddlers are at greatest risk because of their frequent mouthing these objects and their hands that have contacted them (Gurunathan et al. 1998).

Infants and younger children have especially high breathing rates due to their rapid growth and subsequent high levels of oxygen consumption. Their large body surface area per body weight and higher activity levels result in greater energy expenditure for thermogenesis than that required by adults. Children's daily breathing rates used for chronic exposure analysis are approximately twice that of adults (452 vs. 232 L/kg-d) (OEHHA 2000b). Because children are more active than adults, a typical short-term scenario (e.g., one hour or less) might include playing children and sedentary adults. Comparison of the average breathing rates for these two groups finds that a playing child three to twelve years of age may breath 4.5 times as much as a sedentary adult counterpart (OEHHA 2000b).

Bronchioles develop completely prenatally but 85% of alveoli develop in the postnatal period. A newborn infant may have as few as 10 million alveoli vs. 300 million in the adult, representing a greater than 20-fold increase in alveolar surface area. Therefore, when viewed as a dose per lung area, the disparities between the adult and child are even greater than on a body weight basis (Plopper and Thurlbeck 1994).

Young children consume diets with less variety and different preferences than adults. This results in dramatically increased consumption of some items compared with adults. For example, on average non-nursing infants consume over 16 times the average U.S. consumption of apple juice (National Research Council 1993). In addition, young children have higher fluid and food intake rates than adults so that their exposures to contaminants in items they tend to consume is increased even further. For example, total fluid intake decreases from 189 ml/kg/d during the first six months to 35 ml/kg/d in adults (figure 2) (Ershow and Cantor 1989). This results in increased exposure of children to water-borne contaminants relative to adults per unit body weight.

Early childhood is the only time of life when humans consume breastmilk. During the first months it may be the sole source of nutrition. Persistent lipophilic organic chemicals, such as the organochlorine pesticides, are concentrated in breastmilk which is estimated to contain 4% lipid (OEHHA 2000b). Investigators have estimated that 12-14% of the first twenty-five years intake, in terms of toxic equivalents (TEQs), of PCBs and dioxins occurs in the first six months of breastfeeding. The TEQ intake on a picogram/kg-bw basis is 50 times greater in the breastfeeding infant than the adult (Patandin et al. 1999).

Absorption and Volume of Distribution

Characteristics of absorption of chemicals show age-related trends from birth through early childhood. Gastric emptying, pH-dependent passive diffusion, bile acid secretion, and pancreatic enzyme function all may effect absorption of chemicals across the gut wall and may differ with age. Gastric pH is neutral at birth but rapidly decreases over the first postnatal days and approaches adult levels by three months of age. Gastric emptying is erratic in the term newborn and characteristically delayed in the premature. It approaches adult values by 6-8 months. It may be a factor in slowing the rate and extent of absorption (Milsap and Justo 1994); (Kearns and Reed 1989). Bile salt secretion is reduced in newborns compared to adults and may result in decreased absorption of lipid-soluble chemicals (Besunder et al. 1988).

The amount of material absorbed through the lung in any given setting may be increased in a child relative to an adult by virtue of an increased breathing rate per unit body weight. In addition, by the age of three, the alveolar surface area is almost as great as an adult. This provides a large surface per unit body weight relative to an adult for absorption of chemicals into the systemic circulation.

Dermal absorption might also be impacted by age and related physiological differences although this has not been fully characterized.

Total body water as a percentage of body weight decreases from the young fetus to adulthood. At term, water constitutes 75% of body weight and fat constitutes 15%. By six months of age these percentages are 60% and 30%,respectively. The portion of fluid that is extracellular decreases from gestation (65%) to puberty (20%) . As a consequence, water soluble chemicals will tend to have a larger volume of distribution and slower clearance rates in younger infants and children. Fat soluble chemicals will tend to have a smaller volume of distribution, increased blood concentrations, and subsequent relatively more rapid clearance.

Albumin and alpha-1-acid glycoprotein bind xenobiotics and pharmaceuticals in the blood and are found in much lower levels in the neonate and infant. Trichloroacetic acid (TCA), a metabolite of perchloroethylene (PCE) and trichloroethylene (TCE), is very highly bound to albumin (Muller 1972). Lower levels of albumin may result in a larger volume of distribution and also higher unbound TCA in the blood. Additionally, bilirubin and free fatty acids are often present at elevated levels during the first weeks of life and competitively bind with albumin and may displace TCA leading to greater potential for acute toxicity (Ginsberg 2000). The lower concentrations of albumin and total proteins in the blood during infancy do not approach adult values until 10-12 months (Reed 1996).

Metabolism

The ontogeny of metabolic pathway development during early life may result in important changes in rates of activation to toxic intermediates, detoxification, and clearance of xenobiotic compounds.

The total cytochrome P450 content of human liver microsomes is unchanged from fetal life through the first year of post-gestational life and is approximately 1.3 the total adult content (Treluyer et al.1991). Although total content of these enzymes is relatively stable, P450

enzymes can be divided into at least three major groupings: those expressed during fetal life, early neonatal (whose activity surges during the first day), and neonatal (whose activity increases during the weeks to months after birth). CYP1A2, a neonatal enzyme, is undetectable up to 1 month (Cresteil 1998).

There has been some study of the development of human p450 enzymes in the liver but very little research about the timing of development of activity in other tissues. In one study, sex and age related differences in CYP1A1 activity in the human brain were documented (Watzka et al. 1999). During childhood enzyme activity increased dramatically and reached adult levels by puberty. In the lung, animal studies have shown that exposure to environmental toxicants (sidestream tobacco smoke) can alter the developmental profile of cytochrome P450 enzymes inducing earlier activity (Gebremichael et al. 1995). Repair of injured pulmonary Clara cells by toxicants activated by cytochrome p450 enzymes is decreased in the early postnatal period in rabbits and neonatal injury alters bronchiolar organization in the adult (Smiley-Jewell et al. 1998, 2000). In general, the level of inducibility of fetal CYP forms is unknown (Hakkola et al. 1998).

Epoxide hydrolase and some glutathione S-transferases are active in fetal life while other glutathione S transferases and UDP-glucuronyltransferases develop in the months following birth. Activity towards exogenous proteins and bilirubin remains extremely low in neonates less than 10 days of age (Omiencinski et al.1994; Cresteil 1998).

Mitochondrial glycine N-acyltransferase, important in the metabolism of many carboxylic acid xenobiotics, displays only 5-40% of adult activity in the newborn human liver. Activity increases from birth and peaks at 18 months and then is stable to 40 yrs (Mawai et al. 1997).

In the pediatric medical literature the phenomenon of drug-drug interactions is well documented. These interactions may occur by different pharmacokinetic or pharmacodynamic mechanisms. The resulting clinical and toxicologic effects may be unpredictable. For example, when phenytoin is given with alcohol the toxicity of alcohol is increased. When combined with theophylline the effects of both are decreased. When given with anticoagulants the anticoagulant effects may be either increased or decreased. The corresponding literature on drug-toxicant or toxicant-toxicant interactions needs development and is certainly equally complex.

As a result of differing enzyme activity, some chemicals are metabolized by wholly different metabolic pathways at different ages. In infants, theophylline is N-methylated to caffeine. In adults this is a minor pathway, the majority being N-demethylated or C-oxidated to monomethylxanthines or methyl-uric acid. A pattern of metabolism similar to adults is achieved by seven to nine months of age (Reed 1996).

While children in general may be at increased risk for pharmacokinetic/dynamic reasons, subsets of children may be yet more sensitive due to genetic susceptibility. In an elegant set of studies, Perera has shown evidence that there is significant transplacental transfer of polyaromatic hydrocarbons (PAHs) and environmental tobacco smoke constituents from mother to fetus, that PAH DNA adducts in maternal and newborn white blood cells are increased from environmental exposure and that the fetus is more sensitive to genetic damage than the mother. Newborns with a specific restriction length polymorphism (RLFP), CYP 1A1 MspI, had elevated numbers of adducts compared to those without the RLFP(Perera 1999).

Excretion

Glomerular filtration rate (GFR) is 2-4 ml/min at birth and increases rapidly to 8-20 ml/min over the first few days of life. In premature newborns GFR may be as low as 0.6-0.8 ml/min. Adult rates (130 ml/min) are approximated by 3-5 months of age. If GFR is measured by creatinine clearance and is adjusted for surface area approximate adult values are not achieved until the third year of life (Reed 1996), (Bergstein 1996). Tubular secretion is decreased for many drugs in newborns and infants. Decreased clearance and prolonged half-life in serum may be expected during the first six months of life for chemicals which rely on renal excretion for elimination (Besunder et al. 1988).

Critical Period Programming

Biologists have described sensitive time periods during which certain stimuli create irreversible effects that sometimes may not be noted until much later in life. One example is the development of functional sweat glands. While we are all born with approximately the same number of sweat glands, none respond to heat at birth. Gradually, they become functional in response to heat over the first two or three years of life. The hotter the conditions in which we grow up during that time the more sweat glands become activated. By three years of age the functional number of sweat glands are irreversibly fixed and will not change for life (Diamond 1991).

The developing organism with rapid cell proliferation, migration, and differentiation is uniquely sensitive to disruption. In the brain these processes are unidirectional and occur at very specific times for different structures. Prenatal events include closure of the neural tube, proliferation of neurons and migration of cortical neurons. During infancy and early childhood proliferation and migration continue along with synaptogenesis, myelination, and development of the blood-brain barrier. Unlike many tissues, neurons proliferate only during development, and each specific cell type only during a limited period, reducing the ability to repair lost cells and function. Structural maturation of neural pathways, including an increase in the diameter and myelination of axons, continues through adolescence. During adolescence the rate of synaptic pruning peaks. Chemical exposures can have profound effects on all of these neurologic developmental processes (Rodier 1994, 1995; Paus et al. 1999; Golub 2000).

Autism, an impairment of social interaction along with abnormal speech development and unusual behaviors, is associated with exposure to thalidomide. In humans thalidomide is linked to a 30% incidence of development of autism when given on day 20-24 of gestation (but not before or after this time). This corresponds with the production of the first neurons forming the motor nuclei of the cranial nerves to which there was evidence of injury (Rodier et al. 1997). This represents a clear example of how very specific critical periods exist during which irreversible events program future development. The effect of a chemical is dependent on the cellular process that it affects and the structures that may be undergoing that process at the time of exposure. Chemicals may affect multiple processes and multiple chemicals may affect the same process (see Table 1). Ethanol affects migration, differentiation, synaptogenesis and myelination and is capable of causing massive apoptosis during the period of

synaptogenesis/brain growth of the third trimester. Ethanol induces apoptosis, interferes with multiple neurodevelopmental processes and causes Fetal Alcohol Syndrome in the fetus but is relatively nontoxic or even neuroprotective in the adult brain (Rice and Barone 2000; Olney et al. 2000).

The development of the immune system results from a series of carefully timed and coordinated events during embryonic, fetal, and early postnatal life. There is evidence for a number of immunotoxic chemicals that exposure of pregnant animals at doses causing only transient effects in adults produces long lasting or permanent immune deficits in their offspring. Examples of agents for which prenatal exposure appears to produce lifelong immunosuppression include chlordane, benzo[a]pyrene, and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (Holladay and Smialowicz 2000). Other organ systems also show unique long-term consequences of early life chemical exposures that are not seen in the mature animal.

Children's Cancer Risk

Risks of cancer from exposures to carcinogens occurring from conception through puberty can be different than exposures occurring in adulthood. There are observations of moderate increases in the prevalence of leukemia in children, testicular cancer in adolescents and young adults, and indications that brain and other nervous system cancers are increasing in children and young adults. Exposures to carcinogens during *in utero* development and in early childhood have been suggested as causal factors responsible for these increases.

Exposure to a carcinogen early in life may result in a greater lifetime risk of cancer for several reasons. Cancer is a multistage process and the occurrence of the first stages in childhood increases the chance that the entire process will be completed, and a cancer produced, within an individual's lifetime. Tissues undergoing rapid growth and development may be especially vulnerable to carcinogenic agents. During periods of increased cell proliferation there is rapid turnover of DNA, and more opportunity for damage (e.g., DNA breaks, crosslinks, adducts) or alterations (e.g., altered DNA methylation) to result in permanent changes to the DNA (e.g., mutations, altered gene expression), and ultimately, cancer. During early development a greater proportion of the body's cells are relatively undifferentiated stem cells. These represent a large target population of somatic cells capable of eventually passing along permanent changes to the DNA during future cell divisions. During development there may also be a larger percentage of the DNA which is transcriptionally active and thus structurally more exposed and vulnerable to damage or alteration by DNA reactive agents. There may be greater sensitivity to hormonal carcinogens early in life since the development of many organ systems is under hormonal control (e.g., male and female reproductive systems, thyroid control of CNS development).

Evidence in humans of increased cancer risk following *in utero* exposure is provided by increases in the incidence of clear cell adenocarcinoma of the vagina in young women exposed to diethylstilbesterol *in utero* (DES daughters) but not in DES mothers (exposed as adults). Increased cancer risk in humans is also noted resulting from exposures at critical periods during childhood including higher rates of radiation-induced breast cancer among women exposed during puberty, compared with those exposed before or after puberty. Other examples include

higher rates of leukemia and thyroid cancer among individuals exposed to radiation as children, compared with those exposed as adults.

Evidence in experimental animals of increased cancer risk following early in life exposure to carcinogens exists for a number compounds, including urethane, vinyl chloride, DES, and tamoxifen. In the case of urethane, numerous studies in rodents have demonstrated an increased susceptibility of the fetus, neonates and very young animals to urethane-induced cancers (Salmon and Zeise 1991; Kaye and Trainin 1966; Rogers 1951). The basis for this increased susceptibility is thought to be due to relatively low levels of esterases responsible for the detoxification and elimination of urethane in the fetus and newborn. This results in higher blood levels of urethane for longer periods of time, and provides greater opportunity for minor routes of urethane metabolism to occur, metabolically transforming urethane to the ultimate active carcinogen.

Vinyl chloride is another carcinogen for which the effect of age at exposure on tumor outcome has been extensively studied (Maltoni et al. 1981, Drew et al. 1983). In rats exposed as either newborns or 11-week old animals, a significant tumorigenic response was observed in the newborn group (liver angiosarcoma and hepatocellular carcinoma), but not in the 11-week old group (Maltoni et al. 1981). When rats, mice, and hamsters were exposed to vinyl chloride starting between two and 14 months of age, the younger the age at first exposure, the greater the lifetime tumor incidence (Drew et al. 1983). Vinyl chloride has also been shown to induce higher levels of hepatic DNA adducts in young animals as compared with adults (Laib et al. 1989; Swenberg et al. 1992). Age-dependent differences in metabolism, leading to increased formation of DNA-reactive metabolites and increased DNA alkylation, combined with differences in cell proliferation rates, are thought to account for the increased susceptibility of young animals to vinyl chloride carcinogenesis.

Tamoxifen is another carcinogen with estrogenic (and antiestrogenic) effects that has been shown to cause cancers of the female reproductive tract of rats and mice when exposures occur earlier, rather than later in life. When tamoxifen was administered to newborn female mice for the first five days of life, incidences of rare uterine adenocarcinomas of up to 50 % were observed (Newbold et al. 1997). An increase in uterine and other tumors of the reproductive tract was also observed in female mice exposed to tamoxifen *in utero* on gestation days 12-18 (Diwan et al. 1997). While no increase in tumors of the reproductive tract were observed in standard long-term bioassays of rats, with tamoxifen exposures starting at five to six weeks of age (IARC 1996), neonatal exposure on days two through five of life resulted in the development of rare uterine adenocarcinomas and squamous cell carcinomas of the vagina and cervix (Carthew et al. 2000). While the carcinogenic mode of action of tamoxifen in young animals remains unknown, these findings, taken together with the studies of DES, suggest that the developing reproductive tract is particularly sensitive to hormonally active carcinogens.

Implementing the Children's Health Initiative

Ambient Air Quality Standards Review

OEHHA has begun re-evaluating the adequacy of the ambient air quality standards for protecting infants and children. We have conducted focused literature reviews of the criteria air pollutants including ozone, PM10, nitrogen dioxide, carbon monoxide, sulfur dioxide, hydrogen sulfide, and lead. The reviews determined whether there were data indicating health effects near the current California AAQS, whether there were data indicating whether infants and children were more sensitive to effects of the pollutant, as well as how close the measured ambient levels of the criteria air pollutants are to the standard. The reviews were utilized to prioritize the criteria air pollutants into two tiers for detailed review of the AAQS and potential revision. The prioritization document entitled "Adequacy of California Ambient Air Quality Standards: Senate Bill No. 25 – Children's Environmental Health Protection" can be found at www.oehha.ca.gov. The reviews indicated that there are sufficient data, primarily from the epidemiological literature, to be concerned that the AAQS for ozone, PM10, and nitrogen dioxide may not be adequately protective of infants and children. Endpoints in the literature include both short-term and long-term lung function decrement and exacerbation of asthma. These pollutants were placed in the draft report into Tier 1. Tier 2 pollutants were lead, carbon monoxide, sulfur dioxide, and hydrogen sulfide. These were considered to less urgently require review for a variety of reasons. For lead, although the ambient air quality standard itself is insufficiently protective, because lead sources are regulated under our Toxic Air Contaminant program and current ambient air levels are considerably lower than the standard, lead fell into Tier 2. In the case of hydrogen sulfide, the effect, odor annoyance, is not as severe as the effects associated with exposure to other pollutants (e.g., exacerbation of asthma). Sulfur dioxide exposure is associated with asthma exacerbation but the concentrations in California air generally are quite low, and considerably below the standard. Although the literature suggests an increase in low-birth weights at ambient exposures, carbon monoxide fell into Tier 2 because the data for effects near ambient exposures are weaker than for ozone, PM10, or NO_2.

Toxic Air Contaminants

In order to create an initial list of five TACs likely to differentially impact children, we are reviewing the pertinent literature on TACs. The cancer potency factors and acute and chronic Reference Exposure Levels for these five TACs will be re-evaluated for adequacy of protecting children. In addition, Airborne Toxic Control Measures developed by the ARB, will be re-evaluated for adequacy in protecting children. Periodic updating of the list is required in the statute. While there are about 200 chemicals or classes of substances listed in California as TACs, we prioritized based on emissions into the air and available information on toxicity. We are conducting more complete evaluations of 30 of these and will be narrowing the list based on information in the literature. The most important criteria include whether data indicate adverse effects in children or young animals that are qualitatively or quantitatively different than adults, and whether existing data indicate that adverse exposure levels are close to measured levels in ambient air in California.

Risk Assessment Methodology

Perhaps the most difficult task is to incorporate information on differences between infants and children and adults into risk assessment practice. We are exploring the pharmaceutical literature and pediatric literature to better define physiological differences between children and adults. There is enough information on physiological parameters important for physiologically-based pharmacokinetic (PBPK) modeling to develop models using child-specific parameters. Efforts are underway to evaluate these models using prototype TACs and physiological parameters for different ages of infants and children. PBPK models give predictions of how the body handles a particular chemical. The models address issues of internal body or tissue dosimetry, route to route extrapolation and interspecies extrapolation. To date few published models for various environmental pollutants address infant and child exposure in a systematic fashion. This is parallel to toxicity testing in animals which is usually initiated in young adult animals. It seems clear from the preliminary studies of PBPK modeling that infants in the first year of life are likely to show increased dosimetry for a variety of agents. We will be exploring PBPK modeling for human dosimetry that will include a series of infant and child anatomical/physiological profiles to address potentially critical developmental stages e.g., newborn, three, six, and nine months, 1-2 years, 2-8 years, and 8-16 years. Biochemical factors for child adjusted PBPK models may need to be scaled from animal or human adult values but values based on the child metabolism of drugs using similar enzymes will be incorporated if available. As appropriate, subpopulations that may be at greater risk from exposure to a given environmental toxicant should also be included in the analysis.

We are also reviewing all available information on exposure parameters for children and particularly for infants. We have already incorporated information on children's intake rates into our risk assessment methods for site-specific risk assessment. These are available in OEHHA (2000b) on our web page at www.oehha.ca.gov. In this document, we developed (or adopted from the published literature) distributions and point estimates of key intake variables for use in chronic exposure scenarios for breathing rate, breast milk consumption, food consumption (categorized into exposed, leafy, protected and root), fish consumption, drinking water consumption, soil ingestion, and dermal absorption. However, there is a need to obtain data useful for acute exposure scenarios. In addition, while this document represents a huge step forward in more adequately characterizing exposure, more and better data are needed for evaluating specific stages of infancy and early childhood. We are focusing further efforts at obtaining this type of information.

Developmental periods of increased susceptibility of children to toxicants, particularly in the first year of life, need to be incorporated into risk assessment. Currently, if developmental toxicity represents the most sensitive endpoint for a chemical, developmental toxicity studies are incorporated into the risk assessment. Occasionally, such as for teratogens, we are aware from animal studies what stages of gestation are important to induce terata. More frequently, there is a lack of data on precise windows of susceptibility during gestation. It is unusual to have information on postnatal windows of susceptibility from birth through adolescence. Adolescence is a time of profound change for the reproductive and central nervous systems that requires special consideration. These issues are quite difficult to quantitatively evaluate without more and better data.

Our existing risk assessment methods include incorporation of an uncertainty factor of three to ten for interindividual variability in the human population when calculating a Reference Exposure Level (REL) for noncancer toxicological endpoints. A REL is a level at or below which no adverse health effects are anticipated. It has been an underlying assumption that the 10-fold UF protects infants and children. We are evaluating the pharmaceutical and toxicological literature to determine whether a factor of 10 is adequate for protecting infants and children. Information from our PBPK modeling efforts will be helpful to making this determination. In addition, chemical specific information from animal studies will be helpful to determining whether the UF of 10 is adequate. It should be noted that the UF of 10 is often used in conjunction with other UF for interspecies extrapolations and/or with other dosimetric adjustments to account for exposure continuity (see OEHHA, 1999a, 2000a). Hence, our evaluation will consider whether the total uncertainty factor in any given REL calculation is adequate to protect infants and children.

Quantitative cancer risk assessment usually starts either with occupational exposure studies or animal carcinogenicity bioassays. Dose is adjusted for the worker or animal paradigm to an equivalent 24 hour 7 day per week exposure before dose-response assessment is conducted. Most agencies utilize linear extrapolation methods to extrapolate from higher occupational or experimental exposures to lower environmental exposures. We calculate the 95% UCL on the slope of the extrapolated dose-response curve to obtain the cancer potency factor (OEHHA, 1999b). The assumption is that using the 95% UCL on the slope helps to account for sensitive members of the population. More recently, information is being published which relates the potency of carcinogens to age-at-exposure. We will be exploring the utility of age-at-exposure adjustments in quantitative cancer risk assessment.

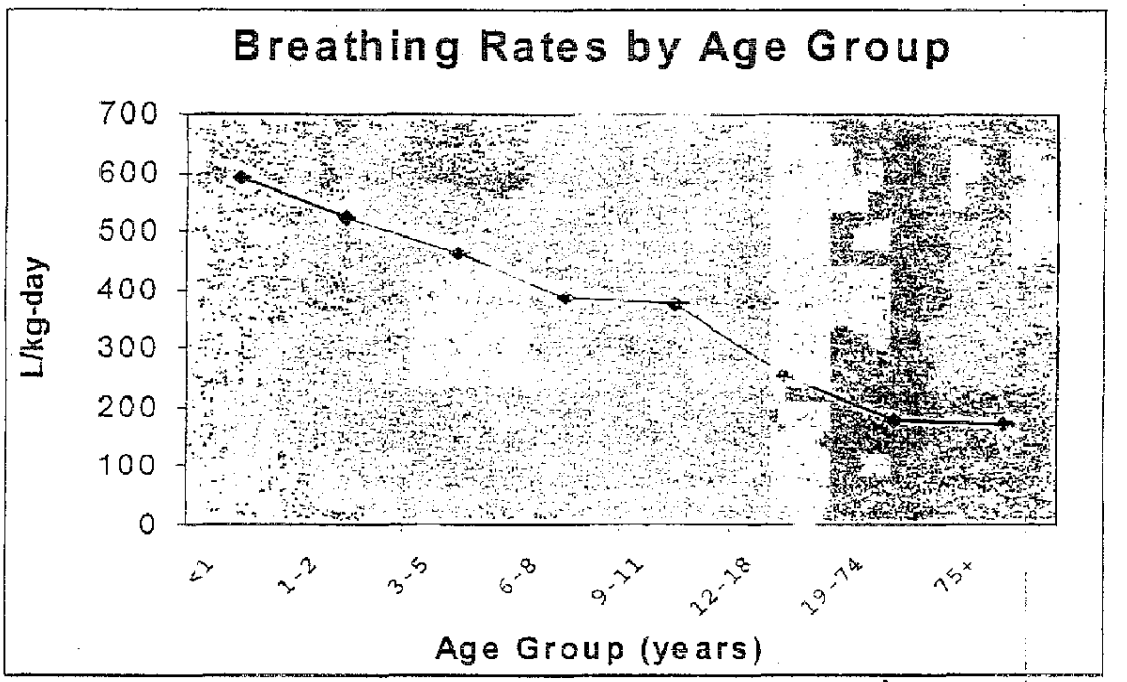
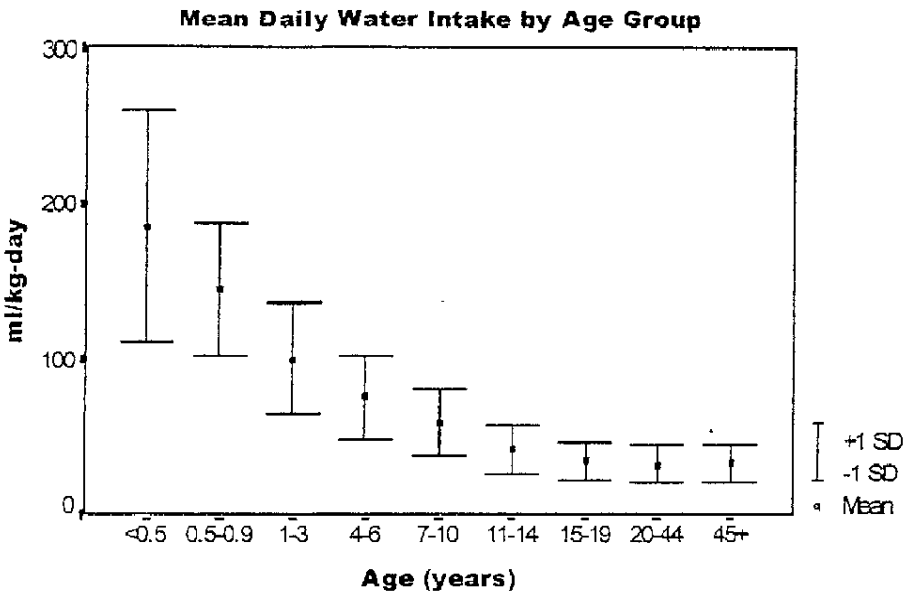


Fig.1 Breathing rates calculated by dividing daily inhalation rates (m^3/day)from Table 5 of Layton (1993) by body weights presented in Table 3 of Layton (1993) (original data from National Food Consumption Survey 1977-1978).



* data from Ershow and Cantor (1989)

Figure 2. Total Mean Daily Water Intake (ml/kg-day) (Ershow and Cantor, 1989). Total water intake includes drinking water and water used in food and beverage preparation.

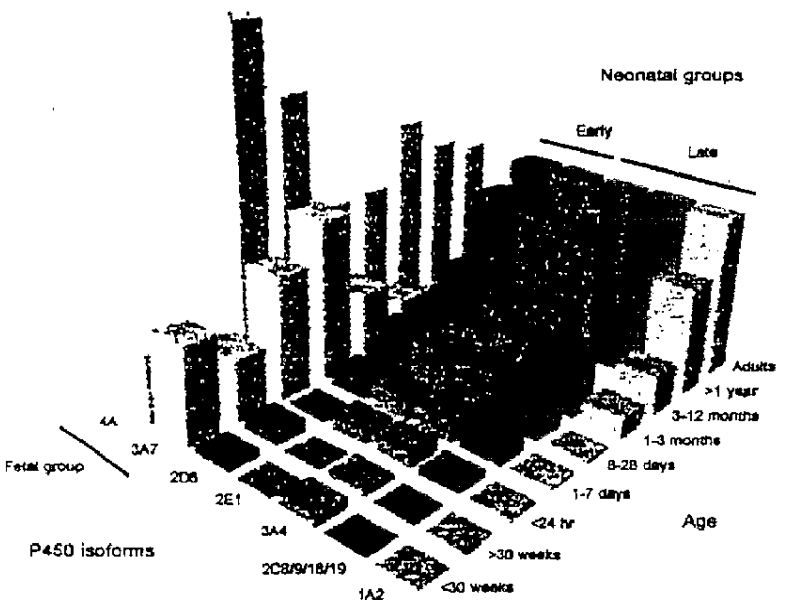


Figure 3. The evolution of cytochrome p450 isoforms in the human Liver (From Cresteil, 1998). Used with permission of Taylor and Francis.

Table 1. Chemicals associated with disruption of neurodevelopmental processes. Based on Rice and Barone, 2000 and Olney, 2000, Environ. Health Perspect.

Process	**Chemicals associated with disruption of this process in animals or humans**
Proliferation	Ionizing radiation, methylazoxymethanol (MAM), ethanol, methyl mercury, chlopyrifos,
Migration	MAM, x-ray radiation, methyl mercury, ethanol
Differentiation	Ethanol, nicotine, methyl mercury, lead
Synaptogenesis	X-ray radiation, ethanol, lead, triethyltin, parathion, polychlorinated biphenyls (PCBs)
Gliogenesis & Myelination	Alterations in thyroid hormone homeostasis, ethanol, lead
Apoptosis	Ethanol, lead, methyl mercury, barbiturates, glutamine, halothane, ketamine
Neurotrophic Signaling	Aluminum, ethanol, cholinesterase inhibitors, methyl mercury

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